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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DUFFY, BRADLEY	

ART UNIT	PAPER NUMBER
1643	

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11/13/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/723,434	ZHONG ET AL.	
	Examiner	Art Unit	
	BRADLEY DUFFY	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-9 and 13-49* is/are pending in the application.

4a) Of the above claim(s) *13-27,29-32 and 40-47* is/are withdrawn from consideration.

5)☒ Claim(s) *7-9,28 and 33-39* is/are allowed.

6)☒ Claim(s) *48-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The examiner of the instant application has changed here at the Patent and Trademark office. Please direct future inquiries concerning this application to Brad Duffy whose telephone number is (571) 272-9935.

2. The amendment filed August 1, 2008, is acknowledged and has been entered. Claims 40-47 have been amended.

3. Claims 7-9 and 13-49 are pending in the application.

4. Claims 13-27, 29-32 and 40-47 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed September 6, 2006.

5. For the reasons explained below, the amendment filed August 1, 2008, amends claims 40-47, so as to be drawn to non-elected inventions. Therefore, Claims 7-9, 28, 33-39 and 48-49 are under examination.

Election/Restriction

6. The amendment filed August 1, 2008, amends claims 40-47, which were previously drawn to the elected invention, so as to be drawn to a non-elected invention.

The claims, as would be amended, are not readable on the elected invention for the following reasons:

The claims, as would be amended, are directed to a product that is a recombinant antibody, which includes antibodies that are not necessarily specific for one epitope on an antigen, such as, e.g., polyclonal antibodies, bispecific antibodies, trispecific antibodies, etc.

In contrast, the claims, which were previously examined, were directed to monoclonal antibodies which are necessarily specific for one epitope on an antigen.

Thus, while the claims, as would be amended, *might* encompass the elected invention, the claims are directed to far broader subject matter, which might include, for example, any recombinant antibody that is not monospecific.

Accordingly, the claims, as would be amended, are drawn to subject matter that was not encompassed by the claims directed to the invention originally examined on the merits.

In this case, the claimed products, as would be amended, such as recombinant polyclonal antibodies, recombinant bispecific antibodies, recombinant trispecific antibodies, etc., are structurally different products which are able to bind multiple epitopes as compared to the originally examined monoclonal antibodies which are specific for one epitope and which were elected by original presentation. Therefore, it is apparent that the subject matter to which the amended claims would be directed is not encompassed by the claims originally examined on the merits.

Furthermore, there would be a serious burden to consider the claims, as would be amended. Notably, the claims, as would be amended, are drawn to an invention not encompassed by the original claims which would require new and different considerations and searches that were not before necessary. Thus, any need to search and consider the claims, as would be amended, would create an undue and serious burden on the Office. Furthermore, the examination of the claims, as would be amended, would require a different search of the prior art and consideration of different non-prior art issues, which were not before required. For example, a thorough search of the technical literature is particularly pertinent in this case and since such a search is performed by a series of key word queries of relevant databases, each search would be performed using a different set or series of key words. For these reasons, any need to search and consider the claims, as would be amended, would create an undue and serious burden on the Office.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits.

Accordingly, claims 40-47 have been withdrawn from consideration as being directed to nonelected inventions. See 37 CFR 1.142(b) and MPEP § 821.03.

Grounds of Rejection Maintained

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 48-49 rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** monoclonal antibodies that specifically bind human VEGF comprising each of the six CDRs of an anti-VEGF antibody that binds human VEGF, or more particularly, three CDRs from the VH domain and three CDRs from the VL domain of the antibody, **does not reasonably provide enablement for using** products commensurate in scope with these claims, such as the recited VH domains or VL domains (as in claims 48 and 49), which as claimed, are not comprised in an antibody as set forth above and do not have any particular function. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

At page 12 of the amendment filed August 1, 2008, Applicant has traversed this ground of rejection.

Applicant's arguments traversing the ground of rejection set forth in the preceding Office action have been carefully considered but not found persuasive to obviate this rejection.

M.P.E.P. § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention commensurate in scope with these claims at the time the application was filed without undue and/or unreasonable experimentation.

Applicant has argued at page 12 of the response filed August 1, 2008, that one of skill in the art could make antibodies that bind VEGF which comprise the claimed VH domains or VL domains, and therefore appears to be arguing that this enables the skilled artisan to use inventions reasonably commensurate in scope with these claims.

In response, this argument is not found persuasive, because the claims are broadly drawn to a VH domain consisting of an amino acid sequence selected from SEQ ID NOs: 88, 90, 91, 106, 107, 107 and 109 (claim 48) or a VL domain consisting of amino acid sequence selected from SEQ ID NOs:26, 28 and 36 (claim 49). Notably, neither of these claims recite that the VH or VL domain are comprised in an antibody

comprising 6 CDRs from a VEGF antibody nor do they recite that these VH or VH domains have any particular function. Accordingly, the claims broadly encompass e.g., a VH domain consisting of the amino acid sequence of SEQ ID NO:88, which is not comprised in an antibody comprising 6 CDRs from a VEGF antibody without any particular function. Accordingly, because the specification does not teach one of skill in the art how to use a VH or VL domain by itself, and because it is highly unpredictable that a VH or VL domain could be used by itself, it is maintained that undue and unreasonable experimentation would be required to use inventions reasonably commensurate in scope with the claims. Notably, as set forth previously office action, and evidenced by the teachings of Paul, Rudikoff and Colman (all of record), it is well established in the art that the formation of an intact antigen-binding site in an antibody routinely requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope. Thus, it is maintained that undue and unreasonable experimentation would be required by one of skill in the art to use a VH domain by itself or a VL domain by itself, because neither would be expected to have any use by themselves because neither would be expected to retain the ability to bind any antigen. For this reason, one of skill in the art would be subject to undue experimentation to use the claimed VH domains or VL domains.

Furthermore, wherein Applicant argues that one of skill in the art could make and screen antibodies which comprise the recited humanized VH domains or humanized VL domains for antibodies that specifically bind human VEGF pointing to the disclosure at paragraph [0445] and to the prior art of Portolano et al (of record) and Clark et al (of record), Applicant is reminded that enablement is not established by one of skill in the art being able to make and screen for products that could then be used, but that inventions reasonably commensurate in scope with the claims could be made and used by one of skill in the art without undue and unreasonable experimentation. In this case, while it is aptly noted that the recited humanized VH domains or humanized VL domains are not comprised in an antibody, even if the recited humanized VH domains or

humanized VL domains were then combined with a random library of VL domains or VH domains, respectively, to produce a diverse genus of antibodies with diverse structures and functions, one of skill in the art would be subject undue and unreasonable experimentation to use antibodies reasonably commensurate in scope with such diverse antibodies produced with a random library of VL domains or VH domains, respectively, because most of the antibodies in such a diverse genus of antibodies would not bind human VEGF. Accordingly, one of skill in the art would be subject to undue and unreasonable experimentation to identify uses for the antibodies reasonably commensurate in scope with such a diverse genus of antibodies as encompassed by the claims.

Furthermore, while Applicant's argues that the specification and the prior art (i.e., Portolano et al (of record) and Clark et al (of record)) ,teach methods of screening for antibodies that specifically bind an antigen using a specific humanized VH or VL combined with a library of complimentary variable domains, as set forth in the previous office action, the references cited by the applicant refer to identifying a complementary variable chain using a specific domain from a human antibody (Portolano et al) or a mouse antibody (Clackson et al), respectively, but not humanized antibodies as set forth in the claimed amino acid sequences. Furthermore, the passage referred to by Applicant at paragraph [0445], does not disclose screening for antibodies that specifically bind a VEGF antigen using a *specific* humanized VH or VL combined with a library of complimentary variable domains, but mutating a hit library of antibodies with degenerate oligonucleotides and then screening for antibodies that specifically bind human VEGF. Accordingly, because the specification lacks any specific, non general guidance which would allow one of skill in the art to identify complimentary humanized VH or VL domains, respectively, given a specific humanized VL or VH domain amino acid sequence which would result in an antibody that specifically binds the human VEGF antigen, and because the prior art of record does not teach that identifying such complimentary humanized VH or VL domains is routine in the art, it is maintained that one of skill in the art could not make such antibodies without undue and unreasonable

experimentation. However, once again, it is aptly noted that the claims are not limited to such antibodies produced by any screening method.

Applicant is reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

In conclusion, upon careful and complete consideration of Applicant's arguments and the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enabled the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Conclusion

9. Claims 7-9, 28 and 33-39 are found allowable. No other claim is allowed.

10. **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be

calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:30 PM, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

/Stephen L. Rawlings/
Primary Examiner, Art Unit 1643

/bd/
Examiner, Art Unit 1643
November 4, 2008